6.01.18	Scintimammography and Gamma Imaging of the Breast and Axilla		
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Section:	6.0 Radiology	**Page:**	Page 1 of 28

Policy Statement

I. Use of radiopharmaceutical administration and gamma detection (lymphoscintigraphy) for localization of sentinel lymph nodes in individuals with breast cancer may be considered **medically necessary**.

II. Scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (MBI) are considered **investigational** in all applications, including but not limited to their use as an adjunct to mammography or in staging the axillary lymph nodes.

NOTE: Refer to Appendix A to see the policy statement changes (if any) from the previous version.

Policy Guidelines

The most commonly used radiopharmaceutical in breast-specific gamma imaging or molecular breast imaging is technetium 99m (Tc 99m) sestamibi.

The 2013 Breast Imaging Reporting and Data System (BI-RADS) breast assessment and breast tissue categories are summarized in Table PG1.

Table PG1. 2013 BI-RADS Breast Assessment and Breast Tissue Categories

Grading Schema	Category
Assessment categories	
	Incomplete
1	Negative
2	Benign
3	Probably benign
4	Suspicious
5	Highly suggestive of malignancy
6	Known biopsy-proven malignancy
Breast tissue categories	
a	Breasts are almost entirely fatty
b	Scattered areas of fibroglandular density
c	Heterogeneously dense
d	Extremely dense

Source: https://www.acr.org/-/media/ACR/Files/RADS/BI-RADS/BIRADS-Poster.pdf.
BI-RADS: Breast Imaging Reporting and Data System.

The most commonly used radiopharmaceuticals for sentinel lymph node detection using either lymphoscintigraphy or hand-held gamma detection include Tc 99m-labeled colloids (e.g., sulfur colloid).

Coding

See the Codes table for details.

Description

Scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (MBI) use radiotracers with nuclear medicine imaging as a diagnostic tool for abnormalities of the breast. These tests are distinguished by the use of differing gamma camera technology, which may improve

diagnostic performance for detecting small lesions. Breast-specific gamma imaging uses a single-head breast-specific gamma camera and a compression device; whereas, MBI uses dual-head breast-specific gamma cameras that also produce breast compression. Preoperative lymphoscintigraphy and/or intraoperative hand-held gamma detection of sentinel lymph nodes is a method of identifying sentinel lymph nodes for a biopsy after radiotracer injection. Surgical removal of 1 or more sentinel lymph nodes is an alternative to full axillary lymph node dissection for staging, evaluation, and management of breast cancer.

Related Policies

- Magnetic Resonance Imaging for Detection and Diagnosis of Breast Cancer
- Radioactive Seed Localization of Nonpalpable Breast Lesions

Benefit Application

Benefit determinations should be based in all cases on the applicable contract language. To the extent there are any conflicts between these guidelines and the contract language, the contract language will control. Please refer to the member's contract benefits in effect at the time of service to determine coverage or non-coverage of these services as it applies to an individual member.

Some state or federal mandates (e.g., Federal Employee Program [FEP]) prohibits plans from denying Food and Drug Administration (FDA)-approved technologies as investigational. In these instances, plans may have to consider the coverage eligibility of FDA-approved technologies on the basis of medical necessity alone.

Regulatory Status

Several scintillation (gamma) cameras have been cleared for marketing by the FDA through the 510(k) process for "measuring and imaging the distribution of radionuclides in the human body by means of photon detection."[17,] Examples of gamma cameras used in BSGI are the Dilon 6800® (Dilon Technologies) and single-head configurations of Discovery NM750b (GE Healthcare). Dual-head cameras used in MBI include LumaGEM™ (Gamma Medical) (FDA product code IYX) and Discovery NM750b (GE Healthcare).

Tc-99m sestamibi (Sun Pharmaceutical Industries, Lantheus Medical Imaging, Cardinal Health 414, AnazaoHealth, Curium US, Jubilant Draximage) has been approved by the FDA with the following labeling: "Breast Imaging: Technetium TC 99M Sestamibi is indicated for planar imaging as a second-line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass. Technetium TC 99M Sestamibi is not indicated for breast cancer screening, to confirm the presence or absence of malignancy, and it is not an alternative to biopsy."

In 2013, Tc 99m tilmanocept (Lymphoseek; Cardinal Health) was approved by the FDA for use in breast cancer and melanoma as a radioactive diagnostic imaging agent to help localize lymph nodes.

Technetium-99m-sulfur colloid was approved by the FDA through the new drug application (NDA; GE Healthcare, NDA 017456; Mallinckrodt, NDA 017724) process although these products appear to be no longer marketed. In addition, in 2011, Technetium Tc 99m Sulfur Colloid Kit (Sun Pharmaceutical Industries) was approved by the FDA through the NDA process (NDA 017858) for use as an injection to localize lymph nodes in breast cancer patients.

In 2018, the FDA granted approval to Northstar Medical Radioisotopes for its RadioGenix™ System, which produces molybdenum 99, the material used to generate Tc 99m. Previously, molybdenum 99 was only produced from enriched uranium in facilities outside of the United States.

Rationale

Background

Mammography

Mammography is the main screening modality for breast cancer, despite its limitations in terms of less than ideal sensitivity and specificity. Limitations of mammography are a particular issue for women at high-risk of breast cancer, for whom cancer risk exceeds the inconvenience of more frequent screening, starting at a younger age, with more frequent false-positive results. Furthermore, the sensitivity of mammography is lower in women with radiographically dense breasts, which is more common among younger women. The clinical utility of adjunctive screening tests is primarily in the evaluation of women with inconclusive results on mammography. A biopsy is generally performed on a breast lesion if imaging cannot rule out malignancy with certainty. Therefore, adjunctive tests will be most useful in women with inconclusive mammograms if they have a high negative predictive value and can preclude the need for biopsy. Additional imaging for asymptomatic women who have dense breasts and negative mammograms has been suggested, but the best approach is subject to debate. [1,]

Scintimammography

Scintimammography is a diagnostic modality using radiopharmaceuticals to detect breast tumors. After intravenous injection of a radiopharmaceutical, the breast is evaluated using planar imaging. Scintimammography is performed with the patient lying prone, and the camera positioned laterally, which increases the distance between the breast and the camera. Special camera positioning to include the axilla may be included when the area of interest is an evaluation for axillary metastases. Scintimammography using conventional imaging modalities has relatively poor sensitivity in detecting smaller lesions (e.g., <15 mm), because of the relatively poor resolution of conventional gamma cameras in imaging the breast.

Breast-Specific Gamma Imaging

Breast-specific gamma imaging (BSGI) and molecular breast imaging (MBI) were developed to address the poor resolution of conventional gamma cameras. Breast-specific gamma cameras acquire images while the patient is seated in a position similar to that in mammography and the breast is lightly compressed. Detector heads are immediately next to the breast, increasing resolution, and images can be compared with mammographic images. Breast-specific gamma imaging and MBI differ primarily in the number and type of detectors used (e.g., multicrystal arrays of cesium iodide or sodium iodide, or nonscintillating, semiconductor materials, such as cadmium zinc telluride). In some configurations, a detector is placed on each side of the breast and used to compress it lightly. The maximum distance between the detector and the breast is therefore from the surface to the midpoint of the breast. The radiotracer typically used is technetium 99m (Tc 99m) sestamibi, and MBI takes approximately 40 minutes.[2,]

Lymphoscintigraphy and Hand-Held Gamma Detection

Preoperative lymphoscintigraphy and/or intraoperative hand-held gamma detection of sentinel lymph nodes (SLNs) is a method of identifying SLNs for a biopsy after radiotracer injection. Surgical removal of 1 or more SLNs is an alternative to full axillary lymph node dissection for staging evaluation and management of breast cancer. Several trials have compared outcomes following SLN biopsy with axillary lymph node dissection for managing patients who have breast cancer. The National Surgical Adjuvant Breast and Bowel Project trial B-32 examined whether SLN dissection provides similar survival and regional control as full axillary lymph node dissection in the surgical staging and management of patients with clinically invasive breast cancer. This multicenter

randomized controlled trial (RCT) included 5611 women and observed statistically similar results for overall survival, disease-free survival, and regional control based on 8-year Kaplan-Meier estimates.[3,] An additional 3-year follow-up of morbidity after surgical node dissection revealed lower morbidity in the SLN dissection group, including lower rates of arm swelling, numbness, tingling, and fewer early shoulder abduction deficits.[4,] A recent systematic review and meta-analysis by Ram et al (2014) reported no significant difference in overall survival (hazard ratio, 0.94; 95% confidence interval, 0.79 to1.19), no significant difference in disease-free survival (hazard ratio, 0.83; 95% confidence interval, 0.60 to 1.14), and similar rates of locoregional recurrence.[5,] However, axillary node dissection was associated with significantly greater surgical morbidity (e.g., wound infection, arm swelling, motor neuropathy, numbness) than sentinel node biopsy.

Radiopharmaceuticals

Scintimammography, Breast-Specific Gamma Imaging, and Molecular Breast Imaging

The primary radiopharmaceutical used with BSGI or MBI is Tc 99m sestamibi. The product label states that Tc 99m sestamibi is "indicated for planar imaging as a second-line diagnostic drug after mammography to assist in the evaluation of breast lesions in patients with an abnormal mammogram or a palpable breast mass. Technetium Tc-99m sestamibi is not indicated for breast cancer screening, to confirm the presence or absence of malignancy, and it is not an alternative to biopsy."[6,]

Technetium TC-99m tetrofosmin (Myoview™), a gamma-emitter used in some BSGI studies,[7,8,] is approved by the U.S. Food and Drug Administration (FDA) only for cardiac imaging.[9,]

Lymphoscintigraphy and/or Hand-Held Gamma Detection

The primary radiopharmaceuticals used for lymphoscintigraphy include Tc 99m pertechnetate-labeled colloids and Tc 99m tilmanocept (Lymphoseek®).[10,] Whereas, Tc 99m sulfur colloid may frequently be used for intraoperative injection and detection of SLNs using a hand-held gamma detection probe.

Radiation Exposure

Scintimammography, Breast-Specific Gamma Imaging, and Molecular Breast Imaging

The radiation dose associated with BSGI is substantial for diagnostic breast imaging modalities. According to Appropriateness Criteria from the American College of Radiology, the radiation dose from BSGI is 10 to 30 mSv, which is 15 to 30 times higher than the dose from a digital mammogram.[11,] According to the American College of Radiology, at these levels, BSGI is not indicated for breast cancer screening.

According to a study by Hruska and O'Connor (2015; who reported receiving royalties from licensed technologies by an agreement with Mayo Clinic and Gamma Medica), the effective dose from a lower "off-label" administered dose of 240 to 300 MBq (6.5-8 mCi) of Tc 99m sestamibi that is made feasible with newer dual-head MBI systems, is 2.0 to 2.5 mSv. For comparison, the effective dose (i.e., mean glandular dose) of digital mammography is estimated to be about 0.5 mSv.[12,] However, it is important to note that the dose for MBI is given to the entire body. The authors compared this dose with the estimated annual background radiation, which varies worldwide between 2.5 mSv and 10 mSv, and asserted that the effective dose from MBI "is considered safe for use in routine screening." Hendrick (2010) calculated mean glandular doses and lifetime attributable risks of cancer due to film mammography, digital mammography, BSGI, and positron emission mammography (PEM).[13,] The author, a consultant to GE Healthcare and a member of the medical advisory boards of Koning (manufacturer of dedicated breast computed tomography) and Bracco (magnetic resonance contrast agents), used group risk estimates from the Biological Effects of Ionizing Radiation VII report[14,] to assess the risk of radiation-induced cancer and mortality from breast imaging studies. For a patient with average-sized breasts (compressed thickness during mammography of 5.3 cm per breast), estimated lifetime attributable risks of cancer at age 40 were:

- 5 per 100000 for digital mammography (breast cancer only),

- 7 per 100000 for screen-film mammography (breast cancer only),
- 55 to 82 per 100000 for BSGI (depending on the dose of Tc 99m sestamibi), and
- 75 for 100000 for PEM.

Corresponding lifetime attributable risks of cancer mortality at age 40 were:

- 1.3 per 100000 for digital mammography (breast cancer only),
- 1.7 per 100000 for screen-film mammography (breast cancer only),
- 26 to 39 per 100000 for BSGI, and
- 31 for 100000 for PEM.

A major difference in the impact of radiation between mammography and BSGI or PEM is that, for mammography, the substantial radiation dose is limited to the breast. With BSGI and PEM, all organs are irradiated, increasing the risks associated with radiation exposure.

Although the use of BSGI (or MBI) has been proposed for women at high-risk of breast cancer, there is controversy and speculation over whether some women (e.g., those with *BRCA* variants) have a heightened radiosensitivity.[15,16,] If women with *BRCA* variants are more radiosensitive than the general population, studies may underestimate the risks of breast imaging with ionizing radiation (i.e., mammography, BSGI, MBI, positron emission mammography, single-photon emission computed tomography/computed tomography, breast-specific computed tomography, tomosynthesis) in these women. In contrast, ultrasonography and magnetic resonance imaging (MRI) do not use radiation. More research is needed to resolve this issue. Also, the risk associated with radiation exposure will be greater for women at high-risk of breast cancer, whether or not they are more radiosensitive because they start screening at a younger age when the risks associated with radiation exposure are greater. In addition, a large, high-quality, head-to-head comparison of BSGI (or MBI) and MRI would be needed, especially for women at high-risk of breast cancer, because MRI, alternated with mammography, is currently the recommended screening technique.

Notes: The term *molecular breast imaging* is used in different ways, sometimes for any type of breast imaging involving molecular imaging, including PEM, and sometimes it is used synonymously with the term *breast-specific gamma camera*, as used in this review.

Use of single-photon emission computed tomography and positron emission tomography of the breast are not addressed in this review.

Literature Review

Evidence reviews assess whether a medical test is clinically useful. A useful test provides information to make a clinical management decision that improves the net health outcome. That is, the balance of benefits and harms is better when the test is used to manage the condition than when another test or no test is used to manage the condition.
The first step in assessing a medical test is to formulate the clinical context and purpose of the test. The test must be technically reliable, clinically valid, and clinically useful for that purpose. Evidence reviews assess the evidence on whether a test is clinically valid and clinically useful. Technical reliability is outside the scope of these reviews, and credible information on technical reliability is available from other sources.

Promotion of greater diversity and inclusion in clinical research of historically marginalized groups (e.g., People of Color [African-American, Asian, Black, Latino and Native American]; LGBTQIA (Lesbian, Gay, Bisexual, Transgender, Queer, Intersex, Asexual); Women; and People with Disabilities [Physical and Invisible]) allows policy populations to be more reflective of and findings more applicable to our diverse members. While we also strive to use inclusive language related to these groups in our policies, use of gender-specific nouns (e.g., women, men, sisters, etc.) will continue when reflective of language used in publications describing study populations.

Scintimammography, Breast-Specific Gamma Imaging, and Molecular Breast Imaging for Diagnosis

Clinical Context and Test Purpose

The purpose of scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (MBI) is to confirm a diagnosis of breast cancer for women with dense breasts or high-risk for breast cancer and in those with indeterminate breast lesions. These tests are also used in breast cancer to detect residual tumor in individuals who have undergone neoadjuvant therapy or individuals planning for breast-conserving therapy.

Dense Breasts or High-Risk for Breast Cancer

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is women with dense breasts or those at high-risk for breast cancer, as part of routine screening.

Interventions

The imaging techniques being considered in this review are scintimammography, BSGI, and MBI. These procedures use radiotracers, which are injected intravenously, followed by nuclear medicine imaging, to detect abnormalities of the breast. Scintimammography uses planar imaging with the woman lying prone and the camera positioned laterally. If the area of interest includes the axilla, the camera can be positioned to include the axilla. During BSGI and MBI, the individual is seated in a position similar to mammography and the breast is lightly compressed. The differences between these techniques are the number and type of detectors used in the camera.

Comparators

The following tests and practices are currently being used to make decisions about women with dense breasts or high-risk for breast cancer: mammography alone, ultrasonography, or MRI.

Outcomes

The general outcomes of interest are overall survival (OS), disease-specific survival, test validity, and treatment-related morbidity.

True-positives can inform decisions to initiate treatment among newly diagnosed women with breast cancer.

False-positives may lead to unnecessary biopsies in women in need of a definitive diagnosis.

True-negatives may reduce the number of biopsies in women in need of a definitive breast cancer diagnosis.

False-negatives may prevent women from pursuing the necessary evaluations to determine a breast cancer diagnosis.

The time frame of interest for calculating performance characteristics is time to biopsy result. Individuals who forgo biopsy based on test results could miss or delay the diagnosis of cancer. Years of follow-up would be necessary to determine the effects on OS.

Study Selection Criteria

For the evaluation of the clinical validity of gamma imaging in women with dense breasts or at high-risk for breast cancer, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).

- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Observational Studies

Several observational studies have assessed BSGI or MBI in women at high-risk for breast cancer (Tables 1 to 4). With advances in imaging technology, lower doses of Tc 99m sestamibi are feasible. Lower doses of Tc 99m sestamibi were specifically used in MBI procedures in studies by Rhodes et al (2015) and Shermis et al (2016).[18,19,] Higher doses of Tc 99m sestamibi were initially used for BSGI in the Brem et al (2016) study, but lower doses were allowed for 196 patients after a protocol change.[20,]

Table 1. Study Characteristics of Clinical Validity of BSGI or MBI in Women With Dense Breasts or at High-Risk for Breast Cancer

Author (Year)	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Zhang (2020)[21,]	Women with heterogeneously or extremely dense breasts who underwent mammography plus either BSGI or ultrasonography	Retrospective	Surgery or core needle biopsy records	BI-RADS 4 or 5		Assessors blinded to previous analysis of BSGI
Shermis (2016)[19,]	Women with heterogeneously or extremely dense breasts and negative mammograms recommended for supplemental screening with MBI	Retrospective	Biopsy by sonographic guidance (stereotactic or MRI-guided biopsy when not visible by ultrasound)	BI-RADS 0, 3, 4, or 5		
Brem (2016)[20,]	Women at increased breast cancer risk undergoing BSGI for supplemental screening after a negative or probably benign mammogram	Retrospective	Pathologic results of biopsy or follow-up imaging that did not demonstrate evidence of malignancy	BI-RADS 0, 4, or 5		Assessors were not blind to patient history or adjunct imaging studies
Rhodes (2015)[18,]	Women with heterogeneously or extremely dense breasts who underwent mammography, MBI, or mammography in combination with MBI	Prospective	Histopathologic diagnosis from surgical excision or core needle biopsy	BI-RADS 3 to 4	365 days	MBI assessors blind to mammographic and clinical information

Author (Year)	Study Population	Design	Reference Standard	Threshold for Positive Index Test	Timing of Reference and Index Tests	Blinding of Assessors
Rhodes (2011)[22,]	Women with heterogeneously or extremely dense breasts and at additional risk for breast cancer who underwent mammography, MBI, or mammography in combination with MBI	Prospective	Histopathologic diagnosis from surgical excision or core needle biopsy	BI-RADS 0, 4, or 5	365 days	Assessors blind to other radiographic and clinical information
Brem (2005)[23,]	Women at high risk for breast cancer with normal mammographic findings undergoing BSGI	Prospective	Biopsy	BI-RADS 4 to 5		BSGI assessors blind to mammographic and clinical information

BI-RADS: Breast Imaging Reporting and Data System; BSGI: breast-specific gamma imaging; MBI: molecular breast imaging; MRI: magnetic resonance imaging.

Table 2. Results of Clinical Validity Studies of BSGI or MBI in Women With Dense Breasts or at High-Risk for Breast Cancer

Author (Year)	Enrolled N	Final N	Clinical Validity			
			Sensitivity	Specificity	PPV	NPV
Zhang (2020)[21,]		364	Increased by 25.23% with BSGI vs. 22.02% with ultrasonography (mean difference 3.21%; p=.23) in women with false-negative mammograms	Increased by 30.82% with BSGI vs. 20.55% with ultrasonography (mean difference 10.27%; p=.003) in women with false-positive mammograms		
Shermis (2016)[19,]		1696			9.1% (95% CI, 5.4 to 15.0) as a result of 13 malignant lesions of 143 positive MBI findings	
Brem (2016)[20,]		849			6.7% as a result of 14 malignancies per 212 abnormal BSGI findings	
Rhodes (2015)[18,]	1608	1585	Mammography: 23.8% (95% CI, 10.6 to 45.1) MBI: 81.0% (95% CI, 60.0 to 92.3) MBI + mammography: 90.5%	Mammography: 89.1% (95% CI, 87.5 to 90.6) MBI: 93.5% (95% CI, 92.1 to 94.6) MBI + mammography:	Mammography: 2.9% (95% CI, 1.2 to 6.5) MBI: 14.3% (95% CI, 9.1 to 21.7) MBI + mammography: 6.8% (95% CI, 4.4 to 10.4; p=.021 vs.	Mammography: 98.9% (95% CI, 98.2 to 99.3) MBI: 99.7% (95% CI, 99.3 to 99.9) MBI + mammography: 99.8% (95% CI, 99.4 to 100; p<.001

Author (Year)	Enrolled N	Final N	Clinical Validity			
			(95% CI, 71.1 to 97.3; p<.001 vs. mammography alone)	83.4% (95% CI, 81.4 to 85.1; p<.001 vs. mammography alone)	mammography alone)	vs. mammography alone)
Rhodes (2011)[22,]	1007	936	Mammography: 27% (95% CI, 9.7 to 56.6) MBI: 82% (95% CI, 52.3 to 94.9) MBI + mammography: 91% (95% CI, 62.3 to 98.4; p<.016 vs. mammography alone)	Mammography: 91% (95% CI, 88.8 to 92.0) MBI: 93% (95% CI, 91.3 to 94.5) MBI + mammography: 85% (95% CI, 82.8 to 87.3; p<.001 vs. mammography alone)	Mammography: 3% (95% CI, 1.2 to 9.6) MBI: 12% (95% CI, 6.6 to 21.8) MBI + mammography: 8% (95% CI, 4.3 to 13.1; p=.158 vs. mammography alone)	
Brem (2005)[23,]	94	94	100% (95% CI, 22 to 100) based on 2 cancers in 16 positive BSGI findings	85% based on 78 negative BSGI findings in 92 patients without cancer	12.5% based on 2 cancers in 16 positive BSGI findings	100% based on 78 negative BSGI findings in 92 patients without cancer

BSGI: breast-specific gamma imaging; CI: confidence interval; MBI: molecular breast imaging; NPV: negative predictive value; PPV: positive predictive value.

Table 3: Study Relevance Limitations of Observational Studies of BSGI or MBI in Women With Dense Breasts or at High-Risk for Breast Cancer

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Zhang (2020)[21,]	4. Race and ethnicity data not reported for study population	1. Tc 99m sestamibi dosing undefined		3. Predictive values not reported 5. Adverse events of the test not described	
Shermis (2016)[19,]	4. Race and ethnicity data not reported for study population			3. Sensitivity and specificity could not be calculated due to missing data 5. Adverse events of the test not described	
Brem (2016)[20,]	4. Race and ethnicity data not reported for study population			3. Sensitivity and specificity not reported 5. Adverse events of the test not described	
Rhodes (2015)[18,]	4. 98.0% of analysis set reported as White			5. Adverse events of the test not described	
Rhodes (2011)[22,]	4. 88% of analysis set reported as White			5. Adverse events of the test not described	

Study	Population[a]	Intervention[b]	Comparator[c]	Outcomes[d]	Duration of Follow-Up[e]
Brem (2005)[23,]	4. Race and ethnicity data not reported for study population			5. Adverse events of the test not described	

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Population key: 1. Intended use population unclear; 2. Study population is unclear; 3. Study population not representative of intended use; 4. Enrolled populations do not reflect relevant diversity; 5. Other.
[b] Intervention key: 1. Classification thresholds not defined; 2. Version used unclear; 3. Not version currently in clinical use.
[c] Comparator key: 1. Classification thresholds not defined; 2. Not compared to credible reference standard; 3. Not compared to other tests in use for same purpose.
[d] Outcomes key: 1. Study does not directly assess a key health outcome; 2. Evidence chain or decision model not explicated; 3. Key clinical validity outcomes not reported (sensitivity, specificity, predictive values); 4. Reclassification of diagnostic or risk categories not reported; 5. Adverse events of the test not described (excluding minor discomforts and inconvenience of venipuncture or noninvasive tests).
[e] Follow-Up key: 1. Follow-up duration not sufficient with respect to natural history of disease.

Table 4: Study Relevance Design and Conduct Limitations of Observational Studies of BSGI or MBI in Women With Dense Breasts or at High-Risk for Breast Cancer

Study	Selection[a]	Blinding[b]	Delivery of Test[c]	Selective Reporting[d]	Completeness of Follow-Up[e]	Statistical[f]
Zhang (2020)[21,]		1. Assessors only blind to prior BSGI	1. Timing of histopathology not described			
Shermis (2016)[19,]		1. Blinding not described	1. Timing of histopathology not described			2. No statistical tests to compare to alternatives
Brem (2016)[20,]		1. Not blinded	1. Timing of histopathology not described			1. Confidence intervals not reported 2. No statistical tests to compare to alternatives
Rhodes (2015)[18,]						
Rhodes (2011)[22,]						
Brem (2005)[23,]			1. Timing of histopathology not described			2. No statistical tests to compare to alternatives

The study limitations stated in this table are those notable in the current review; this is not a comprehensive gaps assessment.
[a] Selection: 1. Selection not described; 2. Selection not random nor consecutive (i.e., convenience).
[b] Blinding: 1. Not blinded to results of reference or other comparator tests.
[c] Delivery of test: 1. Timing of delivery of index or reference test not described; 2. Timing of index and comparator tests not same; 3. Procedure for interpreting tests not described; 4. Expertise of evaluators not described.
[d] Selective reporting: 1. Not registered; 2. Evidence of selective reporting; 3. Evidence of selective publication.
[e] Completeness of follow up: 1. Inadequate description of indeterminate and missing samples; 2. High number of samples excluded; 3. High loss to follow-up or missing data.
[f] Statistical: 1. Confidence intervals and/or p values not reported; 2. No statistical test reported to compare to alternatives.

Section Summary: Dense Breasts or High-Risk for Breast Cancer

Three prospective studies have compared the incremental difference in diagnostic accuracy when BSGI or MBI is added to mammography in women at increased risk, and both MBI studies were conducted by the same research group.[18,22,23,] Sensitivity was higher with combined BSGI (or MBI) and mammography, but specificity was lower. Studies of women at increased risk of breast cancer and negative mammograms found that a small number of additional cancers were detected. Studies tended to include women at different risk levels (e.g., women with dense breasts and those with *BRCA1*). Moreover, any potential benefits need to be weighed against potential risks of additional radiation exposure and risks from breast biopsy for false-negative findings. Even in studies that used a reduced dose of Tc 99m sestamibi, the effective dose (2.4 mSv) exceeded that of digital mammography (»0.5 mSv) by a factor of 4.8. A recent retrospective study in women with dense breasts compared the addition of ultrasonography or BSGI to mammography. The diagnostic accuracy was assessed by the area under the receiver operating characteristic curve revealing higher accuracy with mammography plus BSGI than mammography plus ultrasound or mammography alone (area under the receiver operating characteristic curve 0.90 vs. 0.83 [p=.0019] and 0.76, respectively).[21,]

Indeterminate or Suspicious Breast Lesions

The following PICO was used to select literature to inform this review.

Populations

The population of interest is women with indeterminate or suspicious breast lesions, to confirm a diagnosis.

Interventions

The imaging techniques being considered in this review are scintimammography, BSGI, and MBI (see explanation under the first indication).

Comparators

The following tests and practices are currently being used to make decisions about women with indeterminate or suspicious breast lesions: mammography spot compression views, ultrasonography, or MRI.

Outcomes

The general outcomes of interest are OS, disease-specific survival, test validity, and treatment-related morbidity.

True-positives can inform decisions to initiate treatment among newly diagnosed women with breast cancer.

False-positives may lead to unnecessary biopsies in women in need of a definitive diagnosis.

True-negatives may reduce the number of biopsies in women in need of a definitive breast cancer diagnosis.

False-negatives may prevent women from pursuing the necessary evaluations to determine a breast cancer diagnosis.

The time frame of interest for calculating performance characteristics is time to biopsy result. Individuals who forgo biopsy based on test results could miss or delay the diagnosis of cancer. Years of follow-up would be necessary to determine the effects on OS.

Study Selection Criteria

For the evaluation of the clinical validity of gamma imaging for indeterminate or suspicious breast lesions, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

Review of Evidence

Cho et al (2016) retrospectively reviewed breast lesions in 162 women diagnosed with BI-RADS category 4 lesions (suspicious) on mammography or ultrasonography.[24,] Patients had subsequently undergone BSGI with Tc 99m sestamibi at 925 to 1110 MBq. Using biopsy-confirmed pathologic evaluation as the criterion standard, 66 (40.7%) of 162 lesions were found to be malignant. The sensitivity and specificity of BSGI were 90.9% (95% confidence interval [CI], 81.3% to 96.6%) and 78.1% (95% CI, 68.5% to 85.9%), respectively. The positive predictive value (PPV) was 74.1% (95% CI, 63.1% to 83.2%) and the negative predictive value (NPV) was 92.6% (95% CI, 84.6% to 97.2%). For lesions of 1 cm or smaller, the sensitivity of BSGI was 88.0% (95% CI, 68.6% to 97.5%) and the specificity was 86.8% (95% CI, 71.9% to 95.6%). For lesions larger than 1 cm, the sensitivity was higher (92.7%; 95% CI, 80.1% to 98.5%) and the specificity was lower (61.5%; 95% CI, 44.6% to 76.6%).

Meissnitzer et al (2015) in Austria evaluated BSGI in the diagnostic workup of 67 patients with 92 suspicious breast lesions identified on mammography and/or ultrasonography.[25,] Biopsy results were obtained as the reference standard in all patients, and 67 (73%) of 92 lesions were malignant. Breast-specific gamma images were interpreted visually and semiquantitatively. Overall BSGI sensitivity and specificity were 90% and 56%, respectively, compared with ultrasound sensitivity and specificity of 99% and 20%, respectively. For lesions smaller than 1 cm, the sensitivity of BSGI was 60%.

Tan et al (2014) assessed the diagnostic accuracy of dual-phase BSGI (at 10 to 15 minutes and at 90 to 120 minutes) in 76 women at a single institution in China who had suspicious breast masses.[26,] On pathologic review, 54 (59%) of 92 tumors were malignant, and 38 (41%) were benign. Using receiver operating characteristic-determined cut points for visual and semiquantitative interpretation, sensitivity and specificity were maximized when a combination of visual and early-phase semiquantitative interpretation was used (85% and 92%, respectively) compared with either analysis or delayed-phase semiquantitative analysis alone.

Spanu et al (2012) assessed the clinical impact of BSGI (using Tc 99m tetrofosmin) in a prospective study of 467 women who had suspicious lesions on physical examination, MRI, ultrasound, or mammogram.[27,] Histopathology reports were obtained in all cases. Breast-specific gamma imaging results were true-positives in 408 of 420 breast cancer patients (sensitivity, 97%), including the detection of multifocal, multicentric and bilateral disease, and were false-negatives in 12 breast cancer patients. Breast-specific gamma imaging results were true-negatives in 40 of 47 patients with benign lesions (specificity, 85%). The authors calculated that BSGI provided additional value compared with mammography in 141 (30%) of 467 patients, 108 with breast cancer and 33 with benign lesions.

Hruska et al (2008) evaluated 150 patients with BI-RADS classification 4 or 5 lesions less than 2 cm identified on mammography or ultrasound who were scheduled for a biopsy. The patients underwent MBI using a dual-head, breast-specific gamma camera.[28,] Results from 3 blinded readers were averaged. In 88 patients, 128 cancer tumors were found. The per-lesion sensitivity with the dual-head

camera was 90% (115/128) for all lesions and 82% (50/61) for lesions of 1 centimeter or less. Overall, MBI specificity (across patients) was 69%. The proportion of patients with cancer in this study was higher than might have been expected in a screening population with suspicious lesions on mammography. This was the case because preference was given to those who had a high suspicion of cancer or were likely to have a multifocal or multicentric disease.

Spanu et al (2008) evaluated 145 consecutive patients scheduled for biopsy with MBI (using Tc 99m tetrofosmin) of suspected breast lesions.[29,] With an 86% prevalence of the disease, the sensitivity of MBI was 98% per patient (100% for tumors >10 mm, 91% for tumors ≤10 mm). Per-lesion specificity was 86%. Four cancers were missed, 3 of which were detected by mammography. The authors suggested using MBI for surgical planning or avoiding biopsy but the NPV (83%) was not high enough to forgo biopsy.

Brem et al (2007) compared BSGI with MRI in 23 women who had 33 indeterminate lesions.[30,] Eight patients had 9 pathologically confirmed cancers. Breast-specific gamma imaging demonstrated a significantly greater specificity (71%; 95% CI, 49% to 87%) than MRI (25%; 95% CI, 11% to 47%; p<.05) and comparable sensitivity (BSGI, 89% [95% CI, 51% to 99%] vs. MRI, 100% [95% CI, 63% to 100%]), PPV (BSGI, 53% [95% CI, 27% to 78%] vs. MRI, 33% [95% CI, 17% to 54%]), and NPV (BSGI, 94% [95% CI, 71% to 100%] vs. MRI, 100% [95% CI, 52% to 100%]). The authors noted that the 100% sensitivity and 25% specificity of MRI was likely due to the small number of cancers in the study.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs. No direct evidence was identified.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Indeterminate or Suspicious Breast Lesions

A number of studies have evaluated the diagnostic accuracy of BSGI (or MBI) of suspicious lesions. Compared with biopsy, the NPV in studies that reported this outcome varied from 83% to 94%. The utility of BSGI in evaluating indeterminate or suspicious lesions must be compared with other modalities that would be used (e.g., spot views ultrasound, MRI) for diagnostic mammography. Given the relative ease and diagnostic accuracy of the criterion standard (biopsy), coupled with the adverse consequences of missing a breast cancer, the NPV of BSGI would have to be extremely high to alter treatment decisions. Because NPV is partially determined by disease prevalence, NPV will be lower in a population of patients with mammographic abnormalities highly suggestive of breast cancer than in a population of patients with mammographic abnormalities not suggestive of breast cancer. Therefore, any clinical utility of BSGI as an adjunct to mammography would vary by type of mammographic abnormalities included in the studies.

Detection of Residual Tumor After Neoadjuvant Therapy

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is women with breast cancer undergoing an evaluation to detect any residual tumor tissue following neoadjuvant therapy.

Interventions
The imaging techniques being considered in this review are scintimammography and BSGI. These procedures use radiotracers, which are injected intravenously, followed by nuclear imaging, to detect abnormalities of the breast. Scintimammography uses planar imaging with the woman lying prone and the camera positioned laterally. If the area of interest includes the axilla, the camera can be positioned to include the axilla. During BSGI, the individual is seated in a position similar to mammography, and the breast is lightly compressed. The differences between these techniques are the number and type of detectors used in the camera.

Comparators
The following tests and practices are currently being used by indication to make decisions about women with breast cancer undergoing screening to detect any residual tumor tissue following neoadjuvant therapy: MRI, fluorine 18 fluorodeoxyglucose positron emission tomography, or ultrasonography.

Outcomes
The general outcomes of interest are OS, disease-specific survival, test validity, and treatment-related morbidity.

True-positives can inform surgical and other management decisions.

False-positives may lead to unnecessary treatment.

True-negatives can inform surgical and other management decisions.

False-negatives may result in incorrect treatment decisions.

For women already diagnosed with breast cancer who are using the tests to guide treatment decisions, years of follow-up are necessary to capture recurrence rates and survival rates.

Study Selection Criteria
For the evaluation of the clinical validity of gamma imaging for detection of residual tumor after neoadjuvant therapy, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Review of Evidence
Systematic Reviews
A systematic review and meta-analysis by Guo et al (2016) identified 14 studies investigating the performance of BSGI with Tc 99m for evaluating the response to neoadjuvant therapy in patients with breast cancer.[31,] In all studies, histopathologic results were obtained after surgery and used as the criterion standard. Study sizes ranged from 14 to 122 patients (N=503 patients). Most studies had fewer than 30 patients. Thirteen studies were prospective and 1 was retrospective. Only 3 studies conducted BSGI both before and after treatment. The sensitivity of BSGI for identifying residual disease ranged from 33% to 100%, with a pooled sensitivity of 86% (95% CI, 78% to 92%). The specificity ranged from 17% to 95%, and the pooled specificity was 69% (95% CI, 64% to 74%).

Retrospective Studies
The largest study included in the Guo et al (2016) systematic review is the retrospective and single-center study by Lee et al (2014).[32,] It evaluated BSGI detection of residual tumor after neoadjuvant chemotherapy (primarily anthracycline and taxane-based) in 122 women who had pathologically

confirmed invasive breast cancer. All patients underwent BSGI and dynamic contrast-enhanced breast MRI after completing neoadjuvant therapy. Surgeons consulted BSGI and MRI for surgical planning (i.e., either breast-conserving therapy [64%] or mastectomy [36%]). Of 122 patients, 104 (85%) had residual disease by pathologic review. Breast-specific gamma imaging sensitivity was 74%, specificity was 72%, NPV was 33%, and PPV was 94%. The sensitivity of BSGI varied by cellularity and size of residual tumor (greater sensitivity with greater cellularity and greater tumor size).

No studies were identified that compared imaging methods (e.g., BSGI vs. MRI or fluorine 18 fluorodeoxyglucose positron emission tomography) for detection of residual tumor after neoadjuvant therapy. In addition, no studies were identified on the clinical utility of BSGI (i.e., changes in patient management strategies, such as the extent of surgery) or in health outcomes (e.g., disease-specific survival).

Section Summary: Detection of Residual Tumor After Neoadjuvant Therapy

A systematic review of studies evaluating BSGI for detecting residual tumor after neoadjuvant therapy found a pooled sensitivity of 86% and a pooled specificity of 69%, compared with histopathologic analysis. No studies were identified that compared the diagnostic accuracy of BSGI with other imaging approaches, or that investigated the impact of BSGI on patient management decisions or health outcomes.

Disease Detection During Preoperative Planning for Breast-Conserving Surgery

The following PICO was used to select literature to inform this review.

Populations

The population of interest is women with breast cancer undergoing preoperative planning to determine eligibility for breast-conserving surgery.

Interventions

The imaging techniques being considered in this review are scintimammography and BSGI (see explanation under the previous indication). These interventions assess breast tumor characteristics to determine whether breast-conserving surgery is appropriate or whether a mastectomy is required to obtain adequate margins.

Comparators

The following tests and practices are currently being used by indication to make decisions about women with breast cancer undergoing planning for breast-conserving surgery: MRI.

Outcomes

The general outcomes of interest are OS, disease-specific survival, test validity, and treatment-related morbidity.

True-positives can inform surgical and other management decisions.

False-positives may lead to unnecessary treatment.

True-negatives can inform surgical and other management decisions.

False-negatives may result in incorrect treatment decisions.

For women already diagnosed with breast cancer who are using the tests to guide treatment decisions, years of follow-up are necessary to capture recurrence rates and survival rates.

Study Selection Criteria

For the evaluation of clinical validity of the gamma imaging for disease detection during preoperative planning for breast-conserving surgery, studies that meet the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard.
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Clinically Valid

A test must detect the presence or absence of a condition, the risk of developing a condition in the future, or treatment response (beneficial or adverse).

No studies were identified evaluating the clinical validity of gamma imaging for disease detection during preoperative planning for breast-conserving surgery.

Clinically Useful

A test is clinically useful if the use of the results informs management decisions that improve the net health outcome of care. The net health outcome can be improved if patients receive correct therapy, more effective therapy, or avoid unnecessary therapy or testing.

Direct Evidence

Direct evidence of clinical utility is provided by studies that have compared health outcomes for patients managed with and without the test. Because these are intervention studies, the preferred evidence would be from RCTs.

Edwards et al (2013) retrospectively assessed changes in the surgical management of 218 women who had breast cancer and were eligible for breast-conserving therapy.[33,] All patients had undergone preoperative BSGI or MRI. Twelve percent of patients who had BSGI and 29% of those who had MRI changed to mastectomy. On pathologic review, no patient who underwent a mastectomy was eligible for breast-conserving therapy. Of patients who received breast-conserving therapy, 15% of those who had BSGI and 19% of those who had MRI required a single re-excision because of positive surgical margins, and 14% and 6%, respectively, required a mastectomy. Based on this retrospective study, the clinical utility of BSGI for guiding surgical decision making in breast cancer patients would appear limited.

Chain of Evidence

Indirect evidence on clinical utility rests on clinical validity. If the evidence is insufficient to demonstrate test performance, no inferences can be made about clinical utility.

Section Summary: Preoperative Planning for Breast-Conserving Surgery

One retrospective study is insufficient to determine the clinical utility of BSGI for guiding surgical decision making in breast cancer patients. In this study, results suggested that MRI identified more patients who were not appropriate candidates for breast-conserving therapy than BSGI. Prospective comparative studies are needed.

Scintimammography, Breast-Specific Gamma Imaging, and Radiopharmaceutical or Gamma Detection to Inform Treatment

Clinical Context and Test Purpose

One purpose of scintimammography, BSGI, and radiopharmaceutical or gamma detection is to inform a treatment plan for women diagnosed with breast cancer. This review evaluates the use of

these procedures among women with breast cancer undergoing screening to detect axillary metastases including those undergoing SLN biopsy.

Detection of Axillary Metastases

The following PICO was used to select literature to inform this review.

Populations

The population of interest is women with breast cancer undergoing evaluation to detect axillary metastases.

Interventions

The imaging techniques being considered in this review are scintimammography and BSGI (see explanation under the third indication).

Comparators

The following tests and practices are currently being used by indication to make decisions about women with breast cancer undergoing evaluation to detect any axillary metastases: surgical node dissection.

Outcomes

The general outcomes of interest are OS, disease-specific survival, test validity, and treatment-related morbidity.

True-positives can inform surgical and other management decisions.

False-positives may lead to unnecessary treatment.

True-negatives can inform surgical and other management decisions.

False-negatives may result in incorrect treatment decisions.

For women already diagnosed with breast cancer who are using the tests to guide treatment decisions, years of follow-up are necessary to capture recurrence rates and survival rates.

Study Selection Criteria

For the evaluation of gamma imaging for the detection of axillary metastases, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Review of Evidence

Systematic Reviews

Regarding the use of scintimammography to detect axillary metastases, a meta-analysis reviewed 45 studies of scintimammography and also reported summary estimates of 83% (95% CI, 82% to 84%) for sensitivity and 85% (95% CI, 83% to 86%) for specificity.[34,] In a review of studies published between 1994 and 1998, Taillefer (1999) showed a sensitivity of 77% and a specificity of 89%.[35,]

Case Series

Several case series using different radiopharmaceuticals have shown sensitivities in the high 80% to 90% range.[36,37,]

Section Summary: Detection of Axillary Metastases

Current evidence on BSGI for detection of axillary metastases includes small studies and systematic reviews of these studies. A meta-analysis of 45 small studies found that pooled sensitivity was 93% and pooled specificity was 85%.The test is not accurate enough to replace surgical nodal dissection. No studies have examined patient outcomes comparing the use of scintimammography to aid in decision making regarding nodal dissection with going directly to nodal dissection.

Sentinel Lymph Node Biopsy for Detection of Axillary Metastases

The following PICO was used to select literature to inform this review.

Populations

The relevant population of interest is women with breast cancer who are undergoing SLN biopsy to detect axillary metastases.

Interventions

The therapy being considered is lymphoscintigraphy and radioactive localization for SLN biopsy. Lymphoscintigraphy and radioactive localization are techniques that map sentinel nodes by identifying the lymph drainage basin, determining the number of sentinel nodes, differentiating the sentinel nodes, and marking the sentinel node over the skin for a biopsy.

Comparators

The following practice is currently being used to make decisions about detecting axillary metastases: injection of blue dye or indocyanine green fluorescence.

Outcomes

The general outcomes of interest are OS, disease-specific survival, test validity, and treatment-related morbidity.

True-positives can inform surgical and other management decisions.

False-positives may lead to unnecessary treatment.

True-negatives can inform surgical and other management decisions.

False-negatives may result in incorrect treatment decisions.

For women already diagnosed with breast cancer who are using the tests to guide treatment decisions, years of follow-up are necessary to capture recurrence rates and survival rates.

Study Selection Criteria

For the evaluation of radiotracers for localization of SLNs, studies that met the following eligibility criteria were considered:

- Reported on the accuracy of the marketed version of the technology (including any algorithms used to calculate scores).
- Included a suitable reference standard (describe the reference standard).
- Patient/sample clinical characteristics were described.
- Patient/sample selection criteria were described.

Review of Evidence

Systematic Reviews

Thongvitokomarn et al (2020) published a meta-analysis comparing radioactive tracer or blue dye with indocyanine green fluorescence including 30 studies (N=4216 SLN procedures).[38,] The analysis evaluated detection rate, number of SLNs removed, and the rate of positive tumors comparing indocyanine green, blue dye, and radioactive tracer. Overall lymph node detection rates (total

number of patients whose SLNs were detected by each tracer divided by total number of patients administered each tracer) were 69% to 100%, 65.6% to 97.1%, and 85% to 100% with indocyanine green, blue dye, and radioactive tracer, respectively. The detection rate was significantly different between indocyanine green and blue dye (odds ratio [OR], 6.73; 95% CI, 4.20 to 10.78) but not between indocyanine green and radiotracer imaging (OR, 0.90; 95% CI, 0.40 to 2.03). The number of SLNs removed were 2.35, 1.92, and 1.72 for indocyanine green, blue dye, and radioactive tracer, respectively. Tumor positive rates were calculated by dividing the number of pathological positive SLNs by the total number of SLNs detected by each tracer and analyzed from 8 studies; 8.5% to 20.7% with indocyanine green, 12.7% to 21.4% with blue dye, and 11.3% to 16% with radiotracer. Goonawardena et al (2020) compared radioactive tracer to indocyanine green fluorescence for SLN biopsy in early-stage breast cancer; 19 studies were included (N=2301).[39,] Overall lymph node detection rates ranged from 81.9% to 100% with indocyanine green fluorescence and 85% to 100% with radiotracer. Sentinel lymph node detection was not different between groups (OR, 0.93; 95% CI, 0.47 to 1.83); there was heterogeneity between studies with I^2=58%; p=.003. Tumor positive detection (sensitivity) based on 11 studies were 65.2% to 100% and 76.9% to 100% for indocyanine green fluorescence and radiotracer, respectively. No difference in sensitivity was found (OR, 1.17; 95% CI, 0.43 to 3.17); there was heterogeneity between studies with I^2=41%; p=.09.

Randomized Controlled Trial

A randomized study by van der Vorst et al (2012) compared Tc 99m radiotracer plus near-infrared fluorescence imaging using indocyanine green with or without the use of a patent blue dye for localization of SLNs.[40,] Twenty-four consecutive breast cancer patients who were all undergoing SLN biopsy were studied. Of the 23 cases with successful SLN mapping, the lymph nodes were both radioactive and fluorescent in 100% of cases, whereas only 84% of the lymph nodes showed blue dye staining. In addition, for 25% of cases, the gamma probe was needed to identify and locate the sentinel nodes during the first 15 minutes of localization.

Nonrandomized Trials

Johnson et al (2011) conducted a single institution study assessing 699 patients with operable breast cancer for SLN biopsy.[41,] Using intraoperative Tc 99m-labeled radiopharmaceutical tracer subareolar injection, the sentinel node was localized in 98.6% of cases.

Martin et al (2000) reported a prospective multi-institutional study examining 758 patients who were clinical stage T1-2, N0, M0 invasive breast cancer and who received radioactive colloid and isosulfan blue dye injections before axillary SLN biopsy.[42,] Localization of sentinel nodes was successful in 89% of cases, and 33% of histologically positive SLNs showed no blue dye staining.

Some studies have examined whether preoperative lymphoscintigraphy improves sentinel node localization and detection in clinically node-negative patients and have found little or no incremental value for lymphoscintigraphy imaging of the axilla.[43,44,45,] Note that lymphoscintigraphy uses planar or tomographic imaging that differs from the use of a hand-held gamma detection probe of radioactive nodes during surgery.

Section Summary: Sentinel Lymph Node Biopsy for Detection of Axillary Metastases

For individuals who have breast cancer, are undergoing SLN biopsy to detect any axillary metastases, and who have received radiopharmaceutical and gamma detection for localization of SLNs, the evidence includes a randomized controlled trial, nonrandomized studies, and systematic reviews.. These studies provide consistent evidence that diagnostic performance using radiopharmaceutical and gamma detection yields high success rates in identifying SLNs. Further, these studies would suggest that diagnostic performance trends toward better detection rates using radiopharmaceuticals as opposed to alternative methods using only blue dye, and similar detection rates with indocyanine green fluorescence.

Supplemental Information

The purpose of the following information is to provide reference material. Inclusion does not imply endorsement or alignment with the evidence review conclusions.

Practice Guidelines and Position Statements

Guidelines or position statements will be considered for inclusion in 'Supplemental Information' if they were issued by, or jointly by, a US professional society, an international society with US representation, or National Institute for Health and Care Excellence (NICE). Priority will be given to guidelines that are informed by a systematic review, include strength of evidence ratings, and include a description of management of conflict of interest.

American College of Obstetricians and Gynecologists

The American College of Obstetricians and Gynecologists (2017) updated its 2011 practice bulletin on breast cancer screening in average-risk women.[46,] There was no discussion or recommendation for scintimammography or any other gamma imaging techniques for routine screening.

American College of Radiology

Appropriateness Criteria from the American College of Radiology rated breast-specific gamma imaging a 1 or 2 (indicating "usually not appropriate" for breast cancer screening), in patients with high or intermediate breast cancer risk (last reviewed in 2021),[11,] palpable breast masses (last reviewed in 2022),[47,] and workup of breast pain (last reviewed in 2018).[48,] Guidelines on screening for breast cancer in above average-risk patients (last reviewed in 2018) do not recommend the use of molecular breast imaging (MBI) for breast cancer screening in any higher-risk population. The guidelines state, "further advances in detector technology to allow lower dosing, more widespread penetration of MBI-guided biopsy capabilities, and additional large prospective trials (to include incidence screening results) will be needed before MBI can be embraced as a screening tool, even in women at elevated risk."[49,] In a 2021 guideline for supplemental breast cancer screening based on breast density, MBI is categorized as "usually not appropriate" regardless of breast density and breast cancer risk.[11,]

American Society of Clinical Oncology

The American Society of Clinical Oncology (2016) reaffirmed its 2014 recommendations on the use of sentinel node biopsy for patients with early-stage breast cancer.[50,] The recommendations were based on randomized controlled trials, systematic reviews, meta-analyses, and clinical practice guidelines from 2012 through July 2016. The recommendations included:

"Women without sentinel lymph node (SLN) metastases should not receive axillary lymph node dissection (ALND). Women with 1 to 2 metastatic SLNs who are planning to undergo breast-conserving surgery with whole-breast radiotherapy should not undergo ALND (in most cases). Women with SLN metastases who will undergo mastectomy should be offered ALND. These 3 recommendations are based on randomized controlled trials. Women with operable breast cancer and multicentric tumors, with ductal carcinoma in situ, who will undergo mastectomy, who previously underwent breast and/or axillary surgery, or who received preoperative/neoadjuvant systemic therapy may be offered SNB [sentinel node biopsy]. Women who have large or locally advanced invasive breast cancer (tumor size T3/T4), inflammatory breast cancer, or ductal carcinoma in situ (when breast-conserving surgery is planned) or are pregnant should not undergo SNB."

National Comprehensive Cancer Network

The National Comprehensive Cancer Network's guidelines (v.4.2024) on breast cancer treatment state that sentinel lymph node biopsy is the preferred method for axillary lymph node staging if the patient is a candidate for sentinel lymph node biopsy. If the sentinel nodes are found to be negative on pathologic examination, then no further axillary surgery is suggested (category 1 recommendation). [51,]

Network guidelines on breast cancer screening and diagnosis (v4.2024) include the following relevant recommendations:

"There is emerging evidence that breast scintigraphy and contrast-enhanced mammography may improve detection of early breast cancers among females with mammographically dense breasts; current evidence does *not* support their routine use as alternative screening procedures."

"Consider contrast-enhanced mammography (CEM) or molecular breast imaging (MBI) whole breast ultrasound for those who qualify for but cannot undergo MRI. Whole breast ultrasound may be done if contrast-enhanced imaging or functional imaging is not available/accessible"
High Risk Individuals (BSCR-A, page 1)

- "In high-risk settings, based on current evidence and considering the FDA safety announcement (gadolinium-based contrast agents), we continue to recommend annual MRI in select populations after shared decision-making. Breast cancer screening MRI may also increase recall and increase benign breast biopsies.
- Abbreviated MRI has a higher cancer detection rate than mammography with tomosynthesis and likely has similar sensitivity compared to full diagnostic protocol breast MRI.
- CEM and MBI are also options for higher risk breast cancer screening. CEM has the risk of iodinated contrast reactions and has a higher breast radiation exposure per exam than standard mammography. MBI has a whole-body effective radiation dose substantially higher than that of mammography.[52,]

U.S. Preventive Services Task Force Recommendations

Not applicable.

Medicare National Coverage

There is no national coverage determination. In the absence of a national coverage determination, coverage decisions are left to the discretion of local Medicare carriers.

Ongoing and Unpublished Clinical Trials

Some currently ongoing trials that might influence this review are listed in Table 5.

Table 5. Summary of Key Trials

NCT No.	Trial Name	Planned Enrollment	Completion Date
Ongoing			
NCT02324387	Tc99m Sestamibi Molecular Breast Imaging	96	Mar 2025
NCT02744053	Multimodality Breast Imaging for the Assessment of Tumor Response to Neoadjuvant Chemotherapy in Triple Negative Breast Cancer Patients	96	Apr 2026
NCT03220893	Density MATTERS [Molecular Breast Imaging (MBI) And Tomosynthesis To Eliminate the ReServoir]	3023 (actual)	Dec 2024
NCT05042687	Comparative Performance of Molecular Breast Imaging (MBI) to Magnetic Resonance Imaging (MRI) of the Breast in Identifying and Excluding Breast Carcinoma in Women at High Risk for Breast Cancer	300	Dec 2024

NCT: national clinical trial.

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Documentation for Clinical Review

Please provide the following documentation:

- History and physical and/or consultation notes including:
- Name of test and reason for testing
- Pertinent diagnoses, treatments and response
- Mammogram or other applicable imaging reports

Post Service (in addition to the above, please include the following):

- Procedure (imaging) report

Coding

This Policy relates only to the services or supplies described herein. Benefits may vary according to product design; therefore, contract language should be reviewed before applying the terms of the Policy.

The following codes are included below for informational purposes. Inclusion or exclusion of a code(s) does not constitute or imply member coverage or provider reimbursement policy. Policy Statements are intended to provide member coverage information and may include the use of some codes for clarity. The Policy Guidelines section may also provide additional information for how to interpret the Policy Statements and to provide coding guidance in some cases.

Type	Code	Description
CPT®	78800	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); planar, single area (e.g., head, neck, chest, pelvis), single day imaging
	78801	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); planar, 2 or more areas (e.g., abdomen and pelvis, head and chest), 1 or more days imaging or single area imaging over 2 or more days
	78803	Radiopharmaceutical localization of tumor, inflammatory process or distribution of radiopharmaceutical agent(s) (includes vascular flow and blood pool imaging, when performed); tomographic (SPECT), single area (e.g., head, neck, chest, pelvis), single day imaging ***(Code revision effective 01/01/2023)***
	78195	Lymphatics and lymph nodes imaging
HCPCS	A4641	Radiopharmaceutical, diagnostic, not otherwise classified
	A9500	Technetium tc-99m sestamibi, diagnostic, per study dose
	A9502	Technetium Tc-99m tetrofosmin, diagnostic, per study dose
	A9520	Technetium tc-99m, tilmanocept, diagnostic, up to 0.5 millicuries
	A9541	Technetium Tc-99m sulfur colloid, diagnostic, per study dose, up to 20 millicuries
	S8080	Scintimammography (radioimmunoscintigraphy of the breast), unilateral, including supply of radiopharmaceutical

Policy History

This section provides a chronological history of the activities, updates and changes that have occurred with this Medical Policy.

Effective Date	Action
02/25/1998	Adopted policy from BCBSA TEC
11/02/2002	Coding Update
01/07/2011	Policy title change from Scintimammography Policy revision with no position change
06/30/2015	Coding update
10/30/2015	Policy title change from Scintimammography/Breast-Specific Gamma Imaging/Molecular Breast Imaging Policy revision with position change
03/01/2017	Policy revision with position change

Effective Date	Action
11/01/2017	Policy revision without position change
11/01/2018	Policy revision without position change
11/01/2019	Policy revision without position change
03/01/2020	Coding update
11/01/2020	Annual review. Policy statement, Literature review updated.
11/01/2021	Annual review. No change to policy statement. Policy guidelines and literature updated.
11/01/2022	Annual review. Policy statement and literature review updated.
03/01/2023	Coding update
11/01/2023	Annual review. No change to policy statement. Literature review updated.
11/01/2024	Annual review. Policy statement, policy guidelines and literature review updated.

Definitions of Decision Determinations

Medically Necessary: Services that are Medically Necessary include only those which have been established as safe and effective, are furnished under generally accepted professional standards to treat illness, injury or medical condition, and which, as determined by Blue Shield, are: (a) consistent with Blue Shield medical policy; (b) consistent with the symptoms or diagnosis; (c) not furnished primarily for the convenience of the patient, the attending Physician or other provider; (d) furnished at the most appropriate level which can be provided safely and effectively to the patient; and (e) not more costly than an alternative service or sequence of services at least as likely to produce equivalent therapeutic or diagnostic results as to the diagnosis or treatment of the Member's illness, injury, or disease.

Investigational/Experimental: A treatment, procedure, or drug is investigational when it has not been recognized as safe and effective for use in treating the particular condition in accordance with generally accepted professional medical standards. This includes services where approval by the federal or state governmental is required prior to use, but has not yet been granted.

Split Evaluation: Blue Shield of California/Blue Shield of California Life & Health Insurance Company (Blue Shield) policy review can result in a split evaluation, where a treatment, procedure, or drug will be considered to be investigational for certain indications or conditions, but will be deemed safe and effective for other indications or conditions, and therefore potentially medically necessary in those instances.

Prior Authorization Requirements and Feedback (as applicable to your plan)

Within five days before the actual date of service, the provider must confirm with Blue Shield that the member's health plan coverage is still in effect. Blue Shield reserves the right to revoke an authorization prior to services being rendered based on cancellation of the member's eligibility. Final determination of benefits will be made after review of the claim for limitations or exclusions.

Questions regarding the applicability of this policy should be directed to the Prior Authorization Department at (800) 541-6652, or the Transplant Case Management Department at (800) 637-2066 ext. 3507708 or visit the provider portal at www.blueshieldca.com/provider.

We are interested in receiving feedback relative to developing, adopting, and reviewing criteria for medical policy. Any licensed practitioner who is contracted with Blue Shield of California or Blue Shield of California Promise Health Plan is welcome to provide comments, suggestions, or concerns. Our internal policy committees will receive and take your comments into consideration.

For utilization and medical policy feedback, please send comments to: MedPolicy@blueshieldca.com

Disclaimer: This medical policy is a guide in evaluating the medical necessity of a particular service or treatment. Blue Shield of California may consider published peer-reviewed scientific literature, national guidelines, and local standards of practice in developing its medical policy. Federal and state law, as well as contract language, including definitions and specific contract provisions/exclusions, take precedence over medical policy and must be considered first in determining covered services. Member contracts may differ in their benefits. Blue Shield reserves the right to review and update policies as appropriate.

Appendix A

POLICY STATEMENT (No changes)	
BEFORE Red font: Verbiage removed	**AFTER** Blue font: Verbiage Changes/Additions
Scintimammography and Gamma Imaging of the Breast and Axilla 6.01.18 **Policy Statement:** I. Use of breast specific gamma detection following radiopharmaceutical administration for localization of sentinel lymph nodes in individuals with breast cancer may be considered **medically necessary**. II. Scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (MBI) are considered **investigational** in all applications, including but not limited to their use as an adjunct to mammography or in staging the axillary lymph nodes.	**Scintimammography and Gamma Imaging of the Breast and Axilla 6.01.18** **Policy Statement:** I. Use of radiopharmaceutical administration and gamma detection (lymphoscintigraphy) for localization of sentinel lymph nodes in individuals with breast cancer may be considered **medically necessary**. II. Scintimammography, breast-specific gamma imaging (BSGI), and molecular breast imaging (MBI) are considered **investigational** in all applications, including but not limited to their use as an adjunct to mammography or in staging the axillary lymph nodes.